Intravenous Itraconazole for Prophylaxis of Systemic Fungal Infections in Patients with Acute Myelogenous Leukemia and High-Risk Myelodysplastic Syndrome Undergoing Induction Chemotherapy

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BACKGROUND. Systemic fungal infections remain the leading cause of mortality in patients with newly diagnosed acute myelogenous leukemia (AML) and high-risk myelodysplastic syndrome (MDS). The objective of the current study was to determine whether intravenous itraconazole (I.V. ITRA) reduced the incidence of probable/proven fungal infections in this group of patients, and compare the results with those of a historic control group treated with fluconazole plus itraconazole capsules (F+I).

METHODS. Patients with AML and high-risk MDS who underwent induction chemotherapy received 200 mg of i.v. itraconazole over 60 minutes every 12 hours during the first 2 days followed by 200 mg given i.v. once daily.

RESULTS. One hundred patients were enrolled, 96 of whom were evaluable. Approximately 48% of the patients in the group of patients treated with IV ITRA as well as in the F+I group completed prophylaxis. Nine patients (9%) in the study group developed either proven/probable fungal infections (Candida *glabrata* in 5 patients, C. *tropicalis* in 1 patient, C *krusei* in 1 patient, and F*usarium* in 2 patients) compared with 3 patients (4%) with proven fungal infection in the historic control group (C. *tropicalis* in 1 patient and A*spergillus* in 2 patients). There were no significant differences noted between the two groups with regard to the percentage of patients who developed proven/probable or possible fungal infection as well as with regard to survival. These results also were obtained after adjusting for relevant prognostic factors (creatinine and bilirubin). The most common toxicity encountered with the use of IV ITRA was NCI Grade 3-4 hyperbilirubinemia (6%).

CONCLUSIONS. Despite its theoretic advantages, the authors found no evidence that IV ITRA is superior to itraconazole capsules, at least when the latter is combined with fluconazole. ***Cancer* 2004;100:568–73.**

KEYWORDS: itraconazole, fluconazole, prophylaxis, fungal infections, leukemia.

Despite the use of antifungal prophylaxis, systemic fungal infections remain the leading cause of mortality in patients with newly diagnosed acute myelogenous leukemia (AML) and high-risk myelodysplastic syndrome (MDS) treated at the University of Texas M.D. Anderson Cancer Center. This pattern has been found to be consistent in series dating from 1973–1979,[1] 1991–1994,[2] and 1995–2000.[3] In the most recent survey, 43% of induction deaths were reported to be related to fungal infections, 36% to pneumonia of unknown pathogen (PUP), 19% to bacterial infections, and 2% to viral infections.[3]

We have used several antifungal prophylaxis regimens (fluconazole, fluconazole plus oral itraconazole, and liposomal amphotericin

B) after AML and high-risk MDS induction therapy. None reduced the mortality rate from fungal infections, although the responsible organisms are now more frequently nonalbicans *Candida* species and *Aspergillus* species. Although active against many pathogenic fungi, itraconazole capsules are reportedly absorbed erratically. The intravenous formulation of itraconazole provides high and consistent plasma concentrations.[4,5] In the current study, we attempted to determine whether IV ITRA reduced the incidence of documented fungal infections and PUP in patients with AML and high-risk MDS who were undergoing induction chemotherapy when compared with a historic control group of patients treated with fluconazole plus itraconazole capsules (F+I).

MATERIALS AND METHODS

Study Group

Adults (age $\geq$ 15 years) undergoing induction chemotherapy between October 2000 and January 2001 for newly diagnosed AML or MDS were eligible. Patients were required to have a serum creatinine level $<$ 3.0 mg/dL; aspartate aminotransferase, alanine aminotransferase, and alkaline phosphatase levels $<$ 5 times the upper limit of normal; total bilirubin $<$ 3.0 mg/dL; and no evidence of deep fungal infection. Patients were considered inevaluable if they received fewer than 3 days of study therapy for reasons other than toxicity or the development of a fungal infection, or if information obtained within the first 24 hours of study therapy documented the presence of a fungal infection. The M. D. Anderson Investigational Review Board approved the study. Informed consent was obtained according to institutional guidelines.

Study Protocol

During the first 2 days of chemotherapy, patients received 200 mg of itraconazole i.v. over 60 minutes every 12 hours. Beginning on Day 3, they were given 200 mg i.v. once daily. Prophylaxis was continued until 1 of the following events occurred: 1) the absolute neutrophil count increased to $> 0.5 \times 10^9$/L on 2 consecutive days; 2) complete response (CR), death, or a change in antileukemia therapy because of persistent disease occurred; 3) a proven or suspected systemic fungal infection occurred according to the European Organization for Research and Treatment of Cancer (EORTC)/ National Institute of Allergy and Infectious Diseases Mycoses Study Group (MSG) fungal infections definitions[6] (patients then were given liposomal amphotericin B at a dose of 5 mg/kg i.v. over 2 hours daily); 4) unacceptable toxicity developed; or 5) 42 days had elapsed from the initial administration of prophylaxis.

All patients received antibacterial prophylaxis with levofloxacin at a dose of 500 mg orally daily and antiviral prophylaxis with valacyclovir at a dose of 500 mg orally daily.

Twenty-eight patients received high-dose cytarabine plus anthracycline as remission induction therapy, 4 patients received fludarabine plus high-dose cytarabine $\pm$ anthracycline, 60 patients received gemtuzumab, and 4 other patients received myelosuppressive therapies.

Historic Control Group

The control group was comprised of 67 patients who underwent induction chemotherapy for the treatment of AML or high-risk MDS between April 1998 and May 1999 and who received the combination of oral F+I. This group was chosen as the control group because of similarities in the study design. All patients received 200 mg of fluconazole (in capsule form) every 12 hours and 200 mg of itraconazole (in capsule form) every 12 hours. Itraconazole was taken with a full meal to ensure maximal absorption. All patients received antibacterial and antiviral prophylaxis with oral levofloxacin at a dose of 500 mg daily and oral valacyclovir at a dose of 500 mg daily.

Sixty-four patients received topotecan plus a high-dose cytarabine-containing regimen and 3 patients received other myelosuppressive therapies.

Definitions

Proven fungal infections were defined by a positive culture for fungus in the blood, lung, or fluid obtained from bronchial alveolar lavage, sinuses, soft tissues, or visceral organs in association with symptoms and signs of infection. All infections in this category would meet the criteria for either proven or probable infection according to the EORTC/MSG definition of fungal infections.[6] Patients were diagnosed with PUP if a culture-negative fever persisted for 3 days despite a change in medication from levofloxacin to imipenem or ceftazidime, and if they developed radiographic findings of pneumonia. Such patients would meet the accepted criteria for possible fungal pneumonia.[6] If fever persisted without any localizing signs, the patient was considered to have fever of unknown origin (FUO).

Statistical Analysis

Data regarding eligible patients were summarized using standard descriptive statistics and frequency tabulation. Associations between categoric variables were assessed via cross-tabulation, the chi-squared test, and the Fisher exact test. Differences in continuous variables (including age, creatinine, albumin, bilirubin, absolute neutrophil counts, days on treatment,

TABLE 1
Patient Characteristics

Parameter	IV ITRA	F + I	*P* value
No. evaluable	96	67	
Age (yrs)			0.055
Mean ± SD	60.4 ± 14.0	56 ± 14.8	
Median (range)	64 (25–89)	57 (19–84)	
Gender, (F/M)	37/59	26/41	0.97
Diagnosis, no. (%)			0.37
AML	68 (71)	43 (64)	
MDS	28 (29)	24 (36)	
Zubrod performance status, no. (%)			0.43
0–2	88 (92)	65 (97)	
≥ 3	8 (8)	2 (3)	
Protected environment, no. (%)	69 (72)	47 (70)	0.81
Infection at the start of prophylaxis, no. (%)[a]	26 (27)	17 (25)	0.81
Creatinine (mg%)			0.014
Median (range)	1.0 (0.3–5.9)	0.9 (0.5–1.4)	
Bilirubin (mg%)			0.09
Median (range)	0.7 (0.3–2.0)	0.6 (0.2–2.7)	
Albumin (mg%)			0.053
Median (range)	3.3 (2.0–4.5)	3.4 (2.0–2.7)	
ANC ($\times 10^9$/L)			0.37
Median (range)	663 (0–61,067)	936 (0–33,258)	
ALC ($\times$ 109/L)			0.78
Median (range)	1422 (324–11,715)	1486 (256–16,260)	
Median days on prophylaxis, (range)	19 (3–41)	16 (3–42)	0.04

IV ITRA: intravenous intraconazole; F + I: fluconazole plus itraconazole; SD: standard deviation; F: female; M: male; AML: acute myelogenous leukemia; MDS: myelodysplastic syndrome; ANC: absolute neutrophil counts at initiation; ALC = absolute lymphocyte counts at initiation.
[a] Includes pneumonia, septicemia, fever of unknown origin, cellulitis, otitis, and urinary tract infection.

and lymphocytes) for the two treatment groups were compared using the Student *t* test.

Univariate and multivariate logistic regression models were employed to assess treatment effect on the rate of fungal infection. Survival curves were estimated using the Kaplan–Meier method. The log-rank test was used to assess the difference in time to survival. The univariate and multivariate Cox proportional hazards regression models were used to assess the relation between the patients' prognostic factors and overall survival. Predictive variables in the Cox model were selected by performing a forward stepwise selection with a *P* value of < 0.05 then allowing any variable (*P* value < 0.05) previously deleted to reenter the final model.

Statistical analysis was performed using SAS 8.0 and S-plus 2000 (SAS Institute, Inc., Cary, NC).

RESULTS

Study Group

Of 100 patients enrolled on study, 96 were evaluable for response and toxicity and were compared with the historic control group. Of the remaining 4 patients, 1 was ineligible for induction chemotherapy, 1 patient withdrew consent for induction chemotherapy, and 2 patients received IV ITRA for fewer than 3 days.

Patients in the IV ITRA group were somewhat older and had very slightly higher pretreatment levels of creatinine and bilirubin and very slightly lower pretreatment albumin levels (Table 1)

Approximately 70% of the patients in both groups received induction chemotherapy in a protective environment.

Outcome of Antifungal Prophylaxis

Forty-eight percent of patients in both groups completed antifungal prophylaxis (Table 2). Patients in the study group received longer prophylaxis than those in the control group ($P = 0.044$). Proven or probable invasive fungal infections were reported to occur in 10 patients (10%) in the IV ITRA group and in 3 patients (4%) in the F+I group ($P = 0.24$). The incidence of PUP (i.e., possible fungal infection) was 7% in the former group and 16% in the latter group ($P = 0.08$). Similar proportions of patients in both groups (24%) had persistent FUO or were withdrawn from the study (10%) because of side effects (adverse clinical events or laboratory abnormalities possibly or most likely related to the study drug).

TABLE 2
Cross-Tabulations of Treatment and Response

Covariate	IV ITRA (n = 96)	F + I (n = 67)	P value
Prophylaxis response, no. (%)			
Completed[a]	46 (48)	32 (48)	
Fever of unknown pathogen	23 (24)	16 (24)	0.87
Pneumonia of unknown pathogen	7 (7)	11 (16)	0.08
Fungal infection	9 (9)	3 (4)	0.24
Proven invasive	9	3	
Interrupted therapy for side effects	10 (10)	5 (8)	0.59
Chemotherapy response, no. (%)			0.098
Complete response	41 (43)	38 (57)	
Resistant	32 (33)	21 (31)	
Death	23 (24)	8 (12)	

IV ITRA: intravenous itraconazole; F + I: fluconazole plus itraconazole.
[a] Remained on initial antifungal prophylaxis until recovery from neutropenia.

TABLE 3
Patients with Proven Invasive Fungal Infection

	IV ITRA	F + I
Patients with yeast infections		
C. glabrata	5	
C. tropicalis	1	1
C. krusei	1	
Trichosporon spp	1	
Patients with mold infections		
Aspergillus spp		2
Fusarium spp	1	
Total	9	3

IV ITRA: intravenous itraconazole; F + I: fluconazole plus itraconazole; C. *glabrata*: Candida *glabrata;* C. *tropicalis*: Candida *tropicalis;* C. krusei: Candida *krusei*; spp: species.

In the study group, nonalbicans *Candida* species (spp.) reportedly caused seven of the nine cases of proven fungal infections (C. *glabrata* in five cases, C. *tropicalis* in one case, and C. k*rusei* in one case) (Table 3). The remaining two cases of proven fungal infection were one case of pneumonia resulting from *Fusarium* spp and one case of disseminated *Trichosporon.* No *Aspergillus* infections were observed. Five of the 7 isolates of *Candida* were reported to have dose-dependant susceptibility to itraconazole; 1 was resistant (c. *glabrata*, minimal inhibitory concentration [MIC] ≥ 8 μg/mL) and another was susceptible.

After accounting for the effects of the indicated prognostic factors, there was no suggestion that the type of antifungal prophylaxis affected the incidence of proven/probable/possible fungal infection (Table 4) or overall survival (Table 5) (Fig. 1). The same was true when proven fungal infection was considered the outcome of interest.

TABLE 4
Multivariate Logistic Regression to Assess Treatment Effect on Proven/Probable/Possible Fungal Infection

Variable	Estimate	SE	P value	OR
Creatinine	0.79	0.37	0.032	2.21
Bilirubin	1.73	0.74	0.019	5.67
Gender (F vs. M)	2.44	0.86	0.005	11.44
Prophylaxis (IV ITRA vs. F + I)	0.33	0.78	0.67	1.38

SE: standard error; OR: odds ratio; M: male; F: female; IV ITRA: intravenous intraconazole; F + I: fluconazole plus intraconazole.

TABLE 5
Multivariate Cox Proportional Hazards Model (Survival)

Variable	Estimate	SD	P value	Total
Age	0.03	0.007	< 0.0001	1.03
Creatinine	0.52	0.17	0.002	1.68
ANC	0.00002	0.000012	0.038	1.00
Prophylaxis (IV ITRA F + I)	−0.12	0.20	0.54	0.89

SD: standard deviation; ANC: absolute neutrophil count; IV ITRA intravenous intraconazole; F + I: fluconazole plus intraconazole.

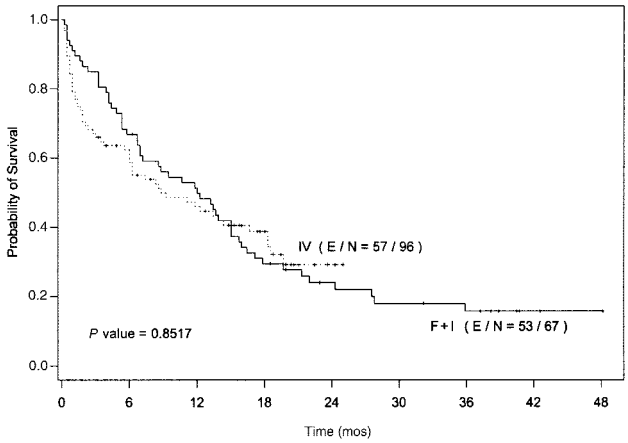

FIGURE 1. Kaplan–Meier estimates of time to survival grouped by treatment. IV ITRA = Intravenous Itraconazole; E = events; N = total; F + I: fluconazole plus itraconazole.

Side Effects

Ten patients (10%) were withdrawn form the study because of side effects or laboratory abnormalities that possibly or most likely were related to the study drug. Hyperbilirubinemia was the most common laboratory abnormality, being reported in six patients, but only four of of these patients (4%) were reported to have $\geq$ Grade 3 toxicity.[14] Only one patient demonstrated a bilirubin decrease after discontinuation of IV ITRA. This suggests that other causes may have contributed to the hyperbilirubinemia, particularly the use of gemtuzumab. Skin rash, possibly related to

TABLE 6
Causes of Death

Causes of death, no. (%)	IV ITRA	F + I
Underlying disease, multiorgan failure	6 (26)	2 (25)
Sepsis	2 (9)	1 (13)
Pneumonia	6 (26)	4 (50)
Documented fungal infection	4 (17%)	1 (13)
Others[a]	5 (22)	0
Total	23	8

IV ITRA: intravenous intraconazole; F + I: fluconazole plus intraconazole.
[a] Others included hemorrhage in two patients, congestive heart failure in one patient, myocardial infarct in one patient, and venooclussive disease in one patient.

itraconazole, was reported to occur in 4 patients (4%). All four of these patients had a reversal after itraconazole was discontinued.

Five patients (8%) in the F+I group were withdrawn from the study because of side effects; in 3 of these patients, the withdrawal was the result of $\geq$ Grade 3 hyperbilirubinemia (4%). There were no significant differences in the incidence of side effects between the study group and the historic control group.

Mortality

The most frequent causes of death in IV ITRA group were failure to respond to chemotherapy (26%) and PUP (26%) (Table 6). Four patients died with persistent fungal infection and prolonged neutropenia despite being treated subsequently with liposomal amphotericin B. Similar to the study group, resistant leukemia (25%) and PUP (50%) were the most frequent causes of death in the control group. Only one patient died of a fungal infection and persistent neutropenia in the F+I group

DISCUSSION

In the current study, we evaluated the efficacy of antifungal prophylaxis with IV ITRA in 96 patients with AML and high-risk MDS who were undergoing induction chemotherapy. The results were compared with those of a historic group of 67 patients who received F+I antifungal prophylaxis. There was no significant difference with regard to the incidence of invasive fungal infection as well as the survival rate between the two groups. Intravenous itraconazole was well tolerated, despite been given for up to 42 consecutive days.

The incidence of documented fungal infections was found to be higher in the current study compared with other similar studies in patients with hematologic malignancies.[7–11] Some of these discrepancies may be accounted for by differences in study design and patient characteristics. In particular, whereas other trials of chemotherapy in patients with AML typically exclude patients with elevated bilirubin or creatinine levels, the current study did not. Therefore, taken together with the association between increased bilirubin and/or creatinine and fungal infection, this finding may help explain the higher rate of fungal infection observed in the current study.

The results of the current study also question the conventional dictum regarding the importance of itraconazole absorption. The objective when using IV ITRA is to ensure that reliable itraconazole concentrations are achieved. The results of the current study suggest that although itraconazole concentrations may be more erratic when administered as capsules rather than in i.v. form, this appears to have little effect on clinical outcome, at least when oral itraconazole is given with fluconazole.

A major problem in interpreting data is the lack of sensitivity/specificity tests used to diagnoses fungal infection. Given this uncertainty, perhaps the most useful outcome to evaluate is survival, although this obviously is affected by factors other than the presence of a fungal infection.[13,14] Especially given the decreasing frequency of autopsies, this problem emphasizes the need to develop better tools for the diagnoses of fungal infection.

The high incidence of nonalbicans C*andida* spp in the group of patients treated with IV ITRA is not unexpected because some of these species exhibit decreased susceptibility to azoles. Itraconazole also is reported to have a higher MIC for most C*andida* spp when compared with fluconazole.

Twelve patients were withdrawn from the study because of toxicity. Hyperbilirubinemia was the most frequent cause of drug discontinuation, although this was believed to be related to the use of itraconazole in only one patient. In the remaining patients, the bilirubin levels did not improve after discontinuation of IV ITRA. This observation suggests other possible etiologies for the liver toxicity such as the chemotherapy regimen used (e.g., gemtuzumab or gemtuzumab chemotherapy combinations). The occurrence of skin reactions also has been reported in other studies.[7,11] Four patients in the current study experienced skin rashes that improved after discontinuation of IV ITRA. Gastrointestinal side effects such as nausea, emesis, and abdominal pain, which are commonly reported with the oral solution of itraconazole,[8,9,11] were absent in the current study.

The data from the current study suggest that IV ITRA antifungal prophylaxis is feasible and safe in patients with AML and high-risk MDS who are undergoing induction chemotherapy. Despite its theoretic advantages, we found no evidence that IV ITRA is

superior to itraconazole capsules, at least when the latter is combined with fluconazole.

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